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(71) Applicant *(for all designated States except US)*: **AERO-MATIC-FIELDER AG** [CH/CH]; Hauptstrasse 145, CH-4416 Bubendorf (CH).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **HANSEN, Ove, Emil** [DK/DK]; Ravnsholtvej 22, DK-3450 Allerød (DK).

(74) Agent: **INTERNATIONALT PATENT-BUREAU**; Høje Taastrup Boulevard 23, DK-2630 Taastrup (DK).

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(54) Title: A PROCESS FOR PRODUCTION OF PARTICLES FOR PHARMACEUTICAL COMPOSITIONS HAVING INCREASED BIOAVAILABILITY

(57) Abstract: A process for production of particles for a pharmaceutical composition having increased bioavailability is disclosed. the process involves spraying a core with a solution or dispersion comprising hydroxypropylmethylcellulose acetate succinate (HPMCAS) and a sparingly water-soluble pharmaceutical active compound in an evaporable liquid, evaporating the liquid to obtain a deposit of HPMCAS and the sparingly water-soluble pharmaceutical active compounds, and repeating the process until a predetermined particle size or weight is obtained.

A PROCESS FOR PRODUCTION OF PARTICLES FOR PHARMACEUTICAL COMPOSITIONS HAVING INCREASED BIOAVAILABILITY

Field of the invention

The present invention relates to a process for production of particles for pharmaceutical compositions having increased bioavailability and a particle obtainable according to said process.

Background of the invention

When a patient receives a dosis form, which may be a tablet, capsule or the like, the pharmaceutical active compound of the dosage form generally enters the blood through a mucosa or the gastro-intestinal channel. In most instances, it is not the entire administered amount of pharmaceutical active compound which is actually absorbed by the body. Various reasons may be the cause for this lack of absorption, including low solubility of the active compound in the relevant body fluid, the dosage form and the fed state of the patient. If the active compound has a poor solubility in the relevant body fluid, the bioavailability is low due to the fact that the active compound to cross the mucosa or the gastric-intestine channel generally has to be in a solubilized state.

Several important pharmaceutical compounds have reduced bioavailability due to a low solubility in body fluids. To increase the bioavailability of such compounds several measures exist, among these the use of a solubility enhancer or the increment of the amorphisity. The amorphisity can be increased by dissolving the pharmaceutical active compound in a solvent and subsequently rapidly evaporate the sol-

vent. The amorphisity can also be enhanced by providing the compound as an amorphous dispersion in a suitable solid carrier, such as a polysaccharide. The present invention is directed to the improvement of the bioavailability of a pharmaceutical active compound by providing the pharmaceutical active compound as a solid dispersion in a derivative of a polysaccharide. Especially, the present is directed to the dispersion of a pharmaceutical active compound in hydroxypropylmethylcellulose acetate succinate (HPMCAS).

US patent No. 4,983,593 discloses a solvate of the drug NZ-105 and HPMCAS. The solvate can be prepared into tablets, capsules, granules, and powders, which exhibit an enhanced bioavailability of the drug. As methods for preparation of the solid solvate, it is suggested to remove the solvent from a solution of NZ-105 and HPMCAS by means of vacuum-drying or freeze-drying. As an alternative, it is suggested to apply a coating on a core filler particle by spraying a solution of NZ-105 and HPMCAS onto the core by means of a fluidized bed granulation method, a centrifugal coating method or a pan coating method.

EP 0 901 786 A2 discloses a composition comprising a dispersion of a sparingly water-soluble drug in HPMCAS. The dispersion is prepared by spray drying a solution of the sparingly water-soluble drug and HPMCAS to form particles with an average diameter less than 100 µm. The spray drying process involves atomizing a solution which comprises the sparingly water-soluble drug, HPMCAS and a suitable solvent into a plurality of small droplets and subsequent removing the solvent from said droplets. It is demonstrated that a supersaturation is obtained for a

number of compounds. However, in the examples, a tendency of the supersaturation not to remain stabile is observed as the degree of supersaturation decreases with time. It is also demonstrated that the supersaturation is not obtained for a composition of the sparingly water-soluble compound and HMPCAS preparred by trituration or simple, slow evaporation of the solvent from a solution of sparingly water-soluble compound and HMPCAS.

Summary of the invention

In a first aspect, the present invention pertains to a process for production of particles for pharmaceutical compositions having increased bio-availability, comprising the steps of:

a) providing a solution or dispersion comprising hydroxypropylmethylcellulose acetate succinate (HPMCAS) and a sparingly water-soluble pharmaceutical active compound in an evaporable liquid,

b) layering a core with one or more deposit(s) comprising HPMCAS and a sparingly water-soluble pharmaceutical active compound by

i) spraying said solution or dispersion onto a core particle suspended in a gas in a chamber,

ii) evaporating the liquid of the solution or dispersion to obtain, on the core particle, a deposit comprising the HPMCAS and the sparingly water-soluble pharmaceutical active compound, and

iii) renewed treatment in accordance with step i) and ii) of the core particle provided with the deposit until a predetermined particle size or weight is obtained, and

c) recovering the particles.

In a second aspect of the present invention a particle is provided which is obtainable in accordance with the above process. In a third aspect of the invention a particle is provided which comprises a core and a layer comprising a solid dispersion of a sparingly water-soluble pharmaceutical active compound in a matrix of hydroxypropylmethylcellulose acetate succinate (HPMCAS)

Detailed description of the invention

The pharmaceutical active compound may be any sparingly water-soluble compound having a pharmaceutical activity, i.e compounds showing therapeutic and/or prophylactic properties when administered to a subject. The term sparingly water-soluble pharmaceutical compound refers herein to a compound which is essentially totally water-insoluble or poorly water-soluble. More specifically, a sparingly water-soluble pharmaceutical compound, as used herein, refers to a compound having a dosage to aqueous solubility greater that 100ml, preferably greater than 500ml, where the aqueous solubility is measured in unbuffered water.

The pure pharmaceutical active compound can be crystalline or amorphous at normal temperatures and pressures. However, the advantages of the present invention is predominantly obtained for compounds that tend to be crystalline at ambient temperatures and pressures.

The term HPMCAS generally refers to a family of cellulose derivatives that can have (1) two types of ether substituents, methyl and/or 2-hydroxypropyl or (2) two types of ester substituents, acetyl and/or

succinyl. HPMCAS is referred to in the scientific literature as O-(2-hydroxypropyl)-O-methyl-cellulose acetate succinate. The degree of substitution for each of the four general types just noted can be varied over a wide range to effect the chemical and physical properties of the polymer. The versatility of HPMCAS allows its structure to be optimized to obtain good performance with a particular pharmaceutical compound of interest. HPMCAS can be purchased commercially. Three examples of commercially available HPMCAS products include Shin-Etsu AQOAT®-LF, Shin-Etsu AQOAT®-MF and Shin-Etsu AQOAT®-HF. All three of these polymers are manufactured by Shin-Etsu Chemical Co., Ltd. (Tokyo). The specific grade that yields the best performance for obtaining and maintaining supersaturation varies depending on the specific chemical and physical properties of the pharmaceutical compound to be delivered. A preferred mean weight average molecular weight range for HPMCAS is 10,000 to 400,000 daltons, as determined using polyethylene oxide standards. Generally, HPMCAS is insoluble in water and gastric fluid but soluble in aqueous base, such as solutions containing sufficient base to have a pH of 6.5 or greater following dissolution of HPMCAS.

The proportion of pharmaceutical active compound to HPMCAS can be within a wide range. As an example, the weight ratio of pharmaceutical active compound to HPMCAS can be between 1 to 0,2 and 1 to 100. The actual proportion used can easily be determined by the person skilled in the art and depend largely on the nature of the pharmaceutical compound used. In some cases is it preferred that the ratio of pharmaceutical active compound to HPMCAS is between 1 to 1 and 1 to 50.

Without wishing to be bound by theory, it is believed that the layering technique used in the present invention effects rapid solvent removal so that crystallization of the pharmaceutical active compound and HPMCAS is largely prevented or at least minimized relative to processes involving solvent removal in a less rapid fashion, such as rotary evaporation. Thus, the present invention provides a process in which the pharmaceutical active compound is efficiently dispersed in a matrix of HPMCAS. Preferably, the pharmaceutical active compound is molecularly dispersed in the HPMCAS matrix, however, a minor amount of local crystallization in the HPMCAS can be accepted.

The solution or dispersion comprising HPMCAS and the pharmaceutical compound may contain further components if so desired. For example, the solution can contain polymers other than HPMCAS that are soluble in the relevant body fluid. Such further polymers include matrix materials such as polyvinylpyrolidone, hydroxypropylcellulose and hydroxypropylmethylcellulose.

A surfactant can also be included in the solution to increase the rate of dissolution of the resulting particle by facilitating wetting and also to inhibit crystallization or precipitation of the pharmaceutical active compound. Examples of surfactants which may be used are fatty acids, alkyl sulfonates, benzethanium chloride, polyoxyethylene sorbitan fatty acid esters (Tween), sodium taurocholic acid, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine, lecithin, and other phospholipids and mono- and diglycerides.

It may also be suitable to include a pH modifier in the solution. pH modifiers can be acids, bases

or puffers. pH modifiers can serve to enhance the dissolution rate for certain pharmaceutical compounds which are more soluble at a specific pH range.

The further components may or may not be fully dissolved in the liquid prior to the layering step.

The liquid for the solution or dispersion in step a) can be any liquid having the ability to dissolve the pharmaceutical compound and swell or dissolve HPMCAS sufficiently to provide a solution or dispersion which is sufficiently stable. The liquid must be sufficient evaporable to allow for an essential removal of liquid during step b) ii) to produce a solidified layer. Preferably, the liquid is non-aqueous and able to provide a true solution of the HPMCAS and the pharmaceutical active compound. A suitable liquid has a boiling point of 150°C or less. The choice of liquid depends on the nature of the components. Suitable liquids are alcohols (methanol, ethanol, n-propanol, iso-propanol, and butanol), ketones (methyl ethyl ketone, acetone, methyl iso-butyl ketone), esters (ethyl acetate, propyl acetate), and various other evaporable liquids such as acetonitril, methylene chloride, toluene, and 1,1,1-trichloroethane. A mixture of two or more liquids may also be used for the solution.

The amount of liquid in the solution can vary within a broad range. Generally, due to process economy, it is desired not to use liquid in a large excess but to use what is needed to provide for a sufficient solution or dispersion. Furthermore, the attached examples tend to show that a more rapid dissolution of the pharmaceutical compound from the final particles results from a solution having a minor amount of liquid relative to a solution having an excess amount of liquid.

The solution or dispersion in step a) is suitably provided by dissolving or swelling the HPMCAS in the solvent and subsequently adding the pharmaceutical active compound under constant stirring. However, the method for providing the solution or dispersion is not critical for the invention.

The cores to be layered with one or more deposit(s) comprising HMPCAS and the pharmaceutical active compound can be pharmaceutically active or pharmaceutically inert. A pharmaceutically active core comprises at least one compound with beneficial prophylactic and/or therapeutic properties when administered to a human or animal subject. The pharmaceutical active compound optionally comprised by the core can be the same compound as the pharmaceutical compound contained in the layer or it can be a different pharmaceutical compound which can be administered simultaneously or subsequent to the administering of the pharmaceutical compound contained in the deposit(s).

A pharmaceutically inert core has substantially no impact on the treated disease of the human or animal body. The pharmaceutical inert core can comprise a disintegrating agent which will cause the layered particle to disrupt in the relevant body fluid. The pharmaceutical inert core can also be a solid particle or object, which does not disintegrate in the relevant body fluid. The pharmaceutical inert core is mainly intended for carrying the layers comprising HPMCAS and the pharmaceutical compound, but the particle or object may have other porposes. Examples of core materials are glass, lactose, microcrystalline cellulose, HPMCAS, and starch.

The cores may have any shape, size, and size distribution suitable for the production of the

desired layered particle. To obtain a uniform final product it is generally desired to use cores with a narrow size distribution. The core may be an agglomerate, a granule, or a particle which has been layered with one or more layer(s) in accordance with the invention. Agglomerates and granules can be made by any method conventionally used in the art, such as spray-drying, vacuum-drying, or spray-granulation. I the event that a particle which has been layered with a layer is used as the core material, such previous prepared layer can contain pharmaceutical active compounds different from or identical to the pharmaceutical active compound incorporated in the layer around this core material.

The cores, which optionally can be layered one or more times, are sprayed with the solution or dispersion comprising HPMCAS and the pharmaceutical active compound in a chamber. The spraying is usually effected by a two fluid or three fluid nozzle while the cores are suspended in a gas. The nozzle can be placed in the top, side walls or the bottom of the spraying chamber and the chamber can be provided with more than one nozzle. It is however, preferred that the nozzle is provided in the bottom to obtain a more even and accurate distribution of the solution on the cores. The best yield is obtained when the direction of the droplets ejected from the nozzle is substantially equal to the direction of the moving cores.

The core particles may be suspended in the gas in any convenient manner. It is, however, preferred that the core particle is carried upwards from the bottom of the spraying chamber by a suitable stream of gas. The gas suspended core particles are then hit by one or more small droplets ejected from the nozzle.

Subsequent to the spraying step, the liquid of the solution provided on the core particles is evaporated to obtain, on the core, a deposit comprising HPMCAS and the pharmaceutical active compound. It is preferred that the chamber in which the spraying is effected also is used for the evaporation of the liquid. In a preferred embodiment, the cores are moved through the spraying zone for performing step b) i) to an evaporation zone for performing step b) ii) by the gas in which the cores are suspended. Furthermore, is it preferred that the gas velocity is high enough to convey the particles out of the chamber.

It is preferred that the gas in which the cores are suspended is drying gas. During the movement upwards in the chamber and following the spraying, the liquid is evaporated. When the cores which have been provided with a deposit comprising HPMCAS and pharmaceutical active compound, leave the chamber and settles, sufficient solvent has preferably been evaporated so that substantial adherence between the individual particles is avoided. As the spraying is effected in the same direction as the movement of the drying gas the spraying method is referred to is the rest of the description as co-current spraying.

The use of co-current spraying has the advantage that the drying can be effected rapidly as the essential drying is done during the relative short period of time the particle is in the upper part of the chamber. It is generally acknowledged, that the degree of amorphisity increases when the evaporation is accelerated, probably due to less time for the individual molecules to arrange in a crystalline form.

Following sufficiently evaporation of the liquid of the solution or dispersion on the core to avoid adherence between the individual particles, the particles may be subjected to a renewed treatment in accordance with step b) i) and b) ii) immediately or the particles may be stored in an interim period before renewed treatment. If the layered particles are stored, it is preferred to store the particles in a compartment adjoining the drying chamber in the same container to allow for a communication between the storage compartment and the spraying chamber. It is preferred slightly to aerate the particles when stored to evaporate any remaining amount of evaporable liquid and to avoid adherence between neighbouring particles.

An improvement of the preferred co-current spraying embodiment can be obtained if the drying gas performs a swirling movement when carrying the particles upwards. Preferably, the swirl in the chamber is essential laminar to avoid non-uniform coating. The swirling causes the particles to move upwards without the occurrence of partial plugging or pulsating or catchy movement through the cloud of atomized solution or dispersion. A preferred apparatus for conducting the process according to the present invention is disclosed in EP 0 741 603 B1 (Aeromatic-Fielder AG), the content of which is incorporated herein by reference.

Another apparatus which can be used for practising the present invention is disclosed in WO 00/40339 (Aeromatic-Fielder AG). According to this disclosure, the cores are initially moved by an upward flow of drying gas and subsequently sprayed with the solution or dispersion which is atomized in a two-fluid or three-fluid nozzle. The drying gas is

supplemented with a muffling gas which impedes the scattering effect of the atomizing gas. The entire disclosure of WO 00/40339 is included herein by reference.

The treatment of the layered particles in step b) continues until a predetermined particle size or weight is obtained. The determination of the desired particle size or weight can be conducted in accordance with known classification procedures. Alternatively, and preferred, a predetermined amount of cores is sprayed with a predetermined amount of solution to produce the particles with the desired particle size or weight.

The particles produced in accordance with the process of the present invention can be formulated into a pharmaceutical composition using methods conventional within the art. Preferred dosage forms are for oral use. Examples of such dosage forms are tablets, capsules, powders, granulates, cachets, and pills. Various additives can be mixed, ground, or granulated with the particles produced according to the invention to form a material which is suitable for the production of the dosage form. Examples of additives are matrix materials, fillers and diluents such as lactose, mannitol, xylitol, microcrystalline cellulose, calcium diphosphate, and starch; surfactants such as lauryl sulfate, and polysorbate 80; complex binding agents or solubilizers such as polyethylene glycols, caffeine, xanthene, and cyclodextrins; disintegrating agents such as sodium starch glycolate, sodium alginate, carboxymethyl cellulose, and methyl cellulose; binders such as methyl cellulose, microcrystalline cellulose, starch, guar gum, and tragacant; lubricants such as magnesium stearate and calcium stearate; and pH modifiers such as acids

(e.g. citric acid, acetic acid, ascorbic acid, lactic acid, aspartic acid, succinic acid, and phosphoric acid), bases (e.g. sodium acetate, potassium acetate, calcium oxide, magnesium oxide, trisodium phosphate, sodium hydroxide, and aluminium hydroxide) and buffers which generally comprise a mixture of an acid or base with the corresponding salt.

Unexpectably, the particles produced in accordance with the present invention show a rapid dissolution rate and an ability to produce a supersaturation in a duodenal mimicing fluid. The supersaturation in the disclosed examples is more than 2 times the normal equilibum concentration for the pharmaceutical active compound. Moreover, the supersaturation is stable in the time span of the analysis (1200 min), that is, no decrease in the amount of dissolved pharmaceutical active compound is observed.

As shown in the examples, the dissolution rate can be altered by altering the ratio of core amount to solution or dispersion comprising HPMCAS and pharmaceutical active compound. Thus, for a fixed amount of pharmaceutical active compound, an increased dissolution rate may be obtained by increasing the amount of core material relative to the amount of solution or dispersion comprising HPMCAS and a pharmaceutical active compound. This effect is probably obtained due to an increased surface area exposed to the duodenal mimicing fluid. This observation makes is possible to design a pharmaceutical composition with a controlled release profile.

EXAMPLES

Example 1

Layering of cores of glass with composition of phenytoin and HMPCAS.

An Aeromatic-Fielder, PRECISION COATER™ MP-1 was used for the production of layered cores. This apparatus is the subject of EP 0 741 603 B1.

Initially, 2 feed materials were prepared by dissolving HPMCAS (Shin-Etsu AQOAT®-MF manufactured by Shin-Etsu Chemical Co., Ltd. (Tokyo)) in acetone in the amounts indicated in table I below under stirring at room temperature (20°C). To this solution the amount of Phenytoin was added under constantly stirring. The stirring was continued until all Phenytoin was dissolved.

Table I:

	Feed material 1	Feed material 2
Phenytoin	30 g	30 g
HPMCAS	270 g	270 g
Acetone	29700 g	2700 g

The core material was selected as glass beads to allow for visual inspection of the produced particles in an optical microscope. The size of the glass beads was 0.5 mm. In run 1 and 2 1500 g of core material was loaded into the PRECISION COATER™ in the storing compartment. The apparatus was started and the core material was brought to the operating temperature of 75°C.

The feed material was sprayed from the bottom with a 2-fluid nozzle at a rate of 30-32 ml/min using

compressed air at 6 bar and a temperature of 75°C. Run 1 was stopped when 12 kg of feed material 1 was used and the Run 2 was continued until all feed material 2 was sprayed onto the cores. Thus, the ratio of core amount to phenytoin in the first run was higher than the amount in the second run.

The layered particles were visually inspected in a optical microscope and a coherent film was observed covering the core particle.

The dissolution of the layers deposited on the cores produced in Run 1 and 2 was tested and compared to a reference of crystalline phenytoin.

A sample was accurately weighed into an empty microcentrifuge tube and 1,8 ml of a phosphate buffered saline solution [(8.2mM NaCl, 1.1 mM Na_2HPO_4, 4.7mM KH_2PO_4, pH 6.5, 290 mOsm/kg) containing 14.7 mM sodium tauocholic acid (Fluka) and 2.8mM 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (Avanti Polar Lipids)] was added to the tube. The phosphate buffered saline solution mimics the duodenal fluid.

The theoretical maximum concentration (TMC) of phenytoin was calculated and is indicated in table II.

The centrifuge tube was closed and a timer was started. The content of the tube was then stirred continuously at the highest speed of a vortex mixer (Fisher Vortex Genie 2) for 60 seconds. The tube was transferred to a centrifuge (Marathon, Model Micro A), allowed to stand undisturbed for six minutes and subsequent centrifuged at 13,000 G for 60 seconds. A 50 µl sample for HPLC analysis was withdrawn from the supernatant in the centrifuge tube via a pipette ten minutes after the timer was started. Solids in the centrifuge tube were resuspended by mixing the sample continuously on the vortex mixer for 60 seconds. The

centrifuge tube was then returned to the centrifuge and allowed to stand undisturbed until the next 50 µl for HPLC analysis was taken. The taking of samples from the centrifuge tube was conducted at 10, 30, 60, 120, 180, and 1200 minutes as described above.

Each sample was diluted with a solution containing 60/40 1.7 % by weight aqueous ammonium acetate/acetonitril. This solution used for the dilution was also used as the mobile phase for the subsequent HPLC analysis.

The concentration of compound was determined by HPLC using a Phenomenex Ultracarb (ODS 20) analytical column. The absorbance was measured at 215 nm with a diode array spectrometer. The measured concentration of compound is indicated in table II.

The gain factor is calculated as the concentration of active compound after 1200 min divided with the concentration of the reference after 1200 min.

Table II:

	Run 1	Run 2	Reference
Sample, mg	53.1	19	9.75
TMC, µg/ml	197	176	5417
Conc. after 10 min	68	26	89
30 min	122	60	78
60 min	156	82	69
120 min	181	109	68
180 min	195	123	72
1200 min	208	149	68
Gain Factor	3.1	2.2	-

The reference was crystalline phenytoin which was placed in excess in a centrifuge tube together

with 1.8ml of the phosphate buffered saline solution. The reference was tested in the same way as the samples. After an initial higher concentration, the soluble amount of phenytoin in the phosphate buffered saline solution stabilizes at a concentration of about 68 µg/ml. This value is considered as the normal saturation point.

It is interesting to observe that the gain factor in Run 1 is over 3 and in Run 2 is more than 2. Thus, using the above process a layered core having an ability to produce a supersaturation under the test conditions is obtained. Moreover, the supersaturation is stable in the time span of the analysis, that is, no decrease in the amount of dissolved phenytoin is observed.

When comparing the results of Run 1 and Run 2, it is noted that the dissolution rate of Run 1 is about twice the dissolution rate of Run 2 within the first 60 min. It is hypothesised that the increased dissolution rate in run 1 is due to an increased surface area and a thinner layer of phenytoin and HMPCAS. This observation makes is possible to design a pharmaceutical composition with a controlled release profile. According to the results, a faster dissolution rate for a certain dosage can be obtained if the ratio of core to phenytoin is increased.

The concentration of solids in Run 1 is 1 % by weight and in Run 2 the concentration is 10 % by weight. It does not seem possible to determine the effect of the amount of solids on the dissolution of phenytoin in the final product.

Example 2

Layering of cores of micro-crystalline cellulose beads with a composition of phenytoin and HPMCAS.

An Aeromatic-Fielder, PRECISION COATER™ PM-1 was used for the layering of cores of spherical microcrystalline cellulose, obtained from Cellphere®, and having a size of 0.5 mm. Feed materials prepared using the procedure described in example 1, and with the composition shown in table III were used.

Table III:

	Feed material 3	Feed material 4
Phenytoin	17.8 g	17.8 g
HPMCAS	160.2 g	160.2 g
Acetone	29700 g	2700 g

890g of the core material was loaded onto the PRECISION COATER™ in each of the two runs with feed material 3 and feed material 4, respectively. The apparatus was started and the core material was brought to the operating temperature of 75°C.

The feed material was sprayed from the bottom with a 2-fluid nozzle at a rate of 30-32 ml/min using compressed air at 6 bar and a temperature of 75°C. All feed material was used for layering the cores.

The obtained layered cores in Run 3 and Run 4 were analysed in accordance with the procedure set forth in example 1. The result of the analysis is shown in table IV below. The gain factor is calculated as defined in example 1.

Table IV:

	Run 3	Run 4	Reference
Sample amount, mg	18.1	18.2	9.75
TMC, µg/ml	168	168	5417
Conc. after 10 min	41	62	89
30 min	62	110	78
60 min	113	158	69
120 min	139	184	68
180 min	146	203	72
1200 min	149	213	68
Gain Factor	2.2	3.1	-

After 1200 min the supersaturation is more than twice the normal saturation for the layered particle produced from the solution having a low content of solids (feed material 3) and more than 3 times the normal saturation for the layered particle produced from the solution having a high content of solids (feed material 4). Also, the dissolution rate in the initial 60 min is higher for the layered particle produced in run 4. It is believed that the increased amount of solvent in feed solution 3 allows for a less degree of amorphisity because more time is available for orientation of the individual species.

It is also interesting to observe that the supersaturation is stable in the time span of the analysis, that is, no decrease in the amount of dissolved phenytoin is observed.

A comparison between the result of example 1 and the present example shows that the material of the core may be of importance for the gain factor. When the particles produced in Run 2 and 4, respecti-

vely, is compared, it is evident that particles having a core of microcrystalline cellulose have a more rapid dissolution profile compared to the particle of Run 2 having a core of glass. A possible explanation may be that solvent during the dissolution test penetrates the layer of phenytoin and HPMCAS and swells the core material, thus increasing the total surface area either by breaking the particle and disrupting the layer or by simply enlarging the particle.

Example 3

Layering of cores of glass with composition of phenytoin and HMPCAS.

A feed material 5 was produced by dissolving 270 g of HPMCAS (Shin-Etsu AQOAT®-MF manufactured by Shin-Etsu Chemical Co., Ltd. (Tokyo)) in 29700 g of acetone under stirring at room temperature (20°C). To this solution 30 g of Phenytoin was added under constant stirring. The stirring was continued until all Phenytoin was dissolved.

1500 g of glass beads having a size of 0.5 mm was loaded into the storage compartment of a PRECISION COATER™ MP-1 (Aeromatic-Fielder). The apparatus was started and the core material was brought to the operating temperature of 75°C.

The entire amount of feed material was sprayed onto the glass beads from the bottom with a 2-fluid nozzle at a rate of 30-32 ml/min using compressed air at 6 bar and a temperature of 75°C.

The obtained layered cores were analysed in accordance with the procedure set forth in example 1. The data for the reference was obtained as depicted

in example 1. The results of the analysis are shown in table V below.

Table V:

	Run 5	Reference
Sample amount, mg	49.2	14.4
TMC, µg/ml	456	8000
Conc. after 10 min	86	83
30 min	129	67
60 min	169	64
120 min	211	70
180 min	224	64
1200 min	245	64
Gain Factor	3.8	-

The sample amount of the layered particles produced in run 5 was selected in the higher area to obtain a TMC which was well above the reference concentration to be able to study the highest possible gain factor. As indicated in table V, a gain factor as high as 3.8 was obtained. Moreover, the supersaturation was stable in the observed time span, indicated by the constant increase in the measured concentration of the phenytoin.

PATENT CLAIMS

1. A process for production of particles for pharmaceutical compositions having increased bioavailability, comprising the steps of:

a) providing a solution or dispersion comprising hydroxypropylmethylcellulose acetate succinate (HPMCAS) and a sparingly water-soluble pharmaceutical active compound in an evaporable liquid,

b) layering a core with one or more deposit(s) comprising HPMCAS and a sparingly water-soluble pharmaceutical active compound by

i) spraying said solution or dispersion onto a core particle suspended in a gas in a chamber,

ii) evaporating the liquid of the solution or dispersion to obtain, on the core particle, a deposit comprising the HPMCAS and the sparingly water-soluble pharmaceutical active compound, and

iii) renewed treatment in accordance with step i) and ii) of the core particle provided with the deposit until a predetermined particle size or weight is obtained, and

c) recovering the particles.

2. The process according to claim 1, wherein a nozzle for spraying in step b) i) is provided in the bottom of the chamber.

3. The process according to claim 2, wherein the direction of the droplets ejected from the nozzle is substantially equal to the direction of the moving cores during the spraying in step b) i).

4. The process according to claim 1, wherein the cores are moved through a spraying zone for

performing step b) i) to an evaporation zone for performing step b) ii) by the gas in which the cores are suspended.

5. The process according to claim 1, wherein the gas in which the cores are suspended is a drying gas.

6. The process according to claim 1, wherein the particles are impeded in an upward scattering movement by a gas flow.

7. The process according to claim 1, wherein the gas in which the cores are suspended performs a swirling movement when carrying the particles upwards from the bottom of the chamber.

8. The process according to claim 1, wherein the dried particles leaving step b) ii), in the interim period, prior to renewed treatment, are stored in an aerated compartment adjoining the chamber.

9. A process for production of particles for pharmaceutical compositions having increased bioavailability, comprising the steps of:

a) providing a solution or dispersion comprising hydroxypropylmethylcellulose acetate succinate (HPMCAS) and a sparingly water-soluble pharmaceutical active compound in an evaporable liquid,

b) layering a core with one or more deposit(s) comprising HPMCAS and a sparingly water-soluble pharmaceutical active compound by

i) spraying, in a chamber, of said solution or dispersion as droplets by a nozzle provided in the bottom of the chamber, onto a core particle moving in an upward direction by a drying gas, whereby the direction of the droplets ejected from

the nozzle is substantially equal to the direction of the moving core particle,

ii) evaporating the liquid of the solution or dispersion to obtain, on the core particle, a deposit comprising the HPMCAS and the sparingly water-soluble pharmaceutical active compound, and

iii) renewed treatment in accordance with step i) and ii) of the core particle provided with the deposit until a predetermined particle size or weight is obtained, and

c) recovering the particles.

10. The process according to claim 9, wherein the dried particles leaving step b) ii), in the interim period, prior to renewed treatment, are stored in an aerated compartment adjoining the chamber.

11. A particle obtainable according to a process for production of particles for pharmaceutical compositions having increased bioavailability, comprising the steps of:

a) providing a solution or dispersion comprising hydroxypropylmethylcellulose acetate succinate (HPMCAS) and a sparingly water-soluble pharmaceutical active compound in an evaporable liquid,

b) layering a core with one or more deposit(s) comprising HPMCAS and a sparingly water-soluble pharmaceutical active compound by

i) spraying said solution or dispersion onto a core particle suspended in a gas in a chamber,

ii) evaporating the liquid of the solution or dispersion to obtain, on the core particle, a deposit comprising the HPMCAS

and the sparingly water-soluble pharmaceutical active compound, and

iii) renewed treatment in accordance with step i) and ii) of the core particle provided with the deposit until a predetermined particle size or weight is obtained, and

c) recovering the particles.

12. The particle according to claim 11, wherein a nozzle for spraying in step b) i) is provided in the bottom of the chamber.

13. The particle according to claim 12, wherein the direction of the droplets ejected from the nozzle is substantially equal to the direction of the moving cores during the spraying in step b) i).

14. The particle according to claim 11, wherein the cores are moved through a spraying zone for performing step b) i) to an evaporation zone for performing step b) ii) by the gas in which the cores are suspended.

15. The particle according to claim 11, wherein the gas in which the cores are suspended is a drying gas.

16. The particle according to claim 11, wherein the particles are impeded in an upward scattering movement by a gas flow.

17. The particle according to claim 11, wherein the gas in which the cores are suspended performs a swirling movement when carrying the particles upwards from the bottom of the chamber.

18. The particle according to claim 11, wherein the dried particle leaving step b) ii), in the interim period, prior to renewed treatment, are stored in an aerated compartment adjoining the chamber.

19. A particle comprising a core and a layer which comprises a solid dispersion of a sparingly

water-soluble pharmaceutical active compound in a matrix of hydroxypropylmethylcellulose acetate succinate (HPMCAS).